therapeutic gene product as opposed to a therapeutic protein. This amendment does not represent new matter and its entry is requested simply to clarify what is meant by the claimed invention. For reasons detailed below, Applicants request that the rejections be withdrawn and pending claims allowed to issue.

1. THE INVENTION

The present invention relates to recombinant adeno-associated virus vectors for gene delivery and regulated tissue specific expression in a host. The vectors of the invention contain a mammalian gene of interest, cis-acting regulatory and promoter elements of the gene of interest and an adeno-associated virus vector comprising the nucleotide sequences encoding the minimal signals of the inverted terminal repeat required for replication, encapsidation, and integration of the viral vector, engineered in such a way that the expression of the gene is regulated in a tissue specific manner by the cis-acting regulatory and promoter elements.

The vectors of the invention may be used to deliver and express a mammalian gene in vivo or ex vivo in a tissue specific manner for both therapeutic and research purposes. The recombinant adeno-associated virus vectors of the present invention may also be used to deliver and express a mammalian gene for research and diagnostic approaches in in vitro cell culture systems.

2. THE CLAIMED INVENTION IS ENABLED WITHIN THE MEANING OF SECTION 112

Claims 1-35 and 39 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. This rejection is in error and should be withdrawn for the reasons set forth below.

To summarize, the Examiner contends that the incorporation of the term "therapeutic" into the claims limits the claims to vectors that are enabled for use in vivo to treat a condition i.e., for use in gene therapy approaches. Having set this very high standard, the Examiner further contends that Applicants have not taught how to use a recombinant adeno-associated virus vector for a therapeutic purpose, i.e., that Applicants have not taught how to achieve successful expression of an introduced gene to a sufficient level to achieve a desired therapeutic effect.

First, gene therapy is not the only stated utility in the specification for the claimed viral vectors, and other utilities including gene transfer for other purposes support utility. Second, the incorporation of the term "therapeutic" into the claims does not limit the claims to vectors that are solely enabled for in vivo uses, but also encompasses the use of the claimed vectors in vitro. The claims are not limited solely to the transfer of therapeutic genes for gene therapy, but rather encompass vectors for the transfer of genes encoding a therapeutic protein to a mammalian cell for research or therapeutic purposes in vitro, in vivo or ex vivo.

Further, the Applicants have clearly demonstrated that the vectors of the claimed invention can be used to successfully transfer a therapeutic gene and achieve expression of that gene in a target mammalian cell in vitro and in vivo.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation from the disclosure in the patent coupled with information known in the art at the time the patent was filed. *U.S. v. Telectronics*, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed.Cir. 1988). Applicants have demonstrated that the instant specification is sufficiently enabling to allow one of ordinary skill in the art to achieve transfer and expression of a transgene in a mammalian cell both in vivo and in vitro utilizing the viral vectors of the present invention.[1]

As exemplified in the working examples of the specification, recombinantly engineered adeno-associated viral vectors were successfully used to introduce and achieve regulated expression of globin gene expression in an erythroid derived cell line (see the instant specification on page 26, lines 24-28). As further exemplified, the recombinantly engineered adeno-associated viral vectors were also successfully used to introduce and express FACC (Fanconi anemia C complementing) cDNA in a lymphoblast cell line (see the instant specification on page 41, lines 9-25).

---

[1] The instant specification, as filed, describes (i) methods for recombinantly engineering adeno-associated virus vectors containing a mammalian gene of interest and the *cis*-acting regulatory and promoter elements of that gene, (ii) methods for transducing the recombinant adeno-associated virus into mammalian cells, and (iii) methods for detecting the expression of the desired gene in the transduced cells.

Additionally, the Examiner's attention is invited to the new Rule 132 Declaration of Dr. Richard Jude Samulski[2] (the "Samulski Declaration"), submitted herewith as Exhibit A. As described in the Samulski Declaration, experiments were conducted in which blood derived cells were isolated, transduced using recombinant adeno-associated virus vectors, and transferred back into a γ-irradiated primate host. As indicated by the data presented in the Samulski Declaration, the transferred viral transgene could be detected in the peripheral blood mononuclear cells (PB) and bone marrow (BM) from three of the six experimental animals (See ¶6, Samulski Declaration). Further, in one experimental animal the transgene could be detected for up to three months following transduction.

Further, the Examiner concurs that the Samulski Declaration demonstrates the successful application of the vectors of the instant invention to achieve detectable expression of the introduced transgene (see the Office Action dated February 13, 1998 at page 4, first paragraph). Thus, applicants have demonstrated (i) the successful adeno-associated virus mediated transfer and tissue specific expression of a globin transgene in erythroid cells, (ii) the successful in vivo transfer of AAV DNA into primate blood derived cells for up to three months following transduction,

---

[2] Applicants invite the Examiner's attention to the Rule 132 Declaration executed by Dr. Richard Jude Samulski submitted herewith. The Declaration submitted herewith has been revised from the previous unexecuted Samulski Declaration submitted on November 21, 1997 in order to clearly indicate that the population of cells which were isolated and successfully transduced by the adeno-associated viral vectors of the present invention are primate blood derived cells.

(iii) that AAV transduction of blood derived cells does not adversely affect reconstitution of the transplanted animals, and (iv) that the transduced cells are capable of expressing a functional protein.

The instant specification, as filed, teaches a number of uses for the recombinant viral vectors of the present invention. For example, the viral vectors of the present invention are not solely useful for the transfer of genes to mammalian cells for therapeutic purposes, but may also be used to transfer genes to mammalian cells for research purposes. Applicants are not required to accomplish all the uses stated in the specification for the claimed compositions of matter. Raytheon Co. v. Roper Corp. 724 F.2d 951 (Fed. Cir. 1983). As such, the Applicants are only required to provide teaching that would enable one of skill in the art to make the claimed compositions and how to achieve at least one of the stated uses of such claimed compositions.

Further, as stated in the M.P.E.P.: "It is common and sensible for an applicant to identify several specific utilities for an invention, particularly where the invention is a product. However, regardless of the category of invention that is claimed, an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. §101 and 35 U.S.C. §112, additional statements of utility do not render the claimed invention lacking in utility. See, e.g., Raytheon v. Roper, 724, F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984), In re Gottlieb, 328 F.2d

1016, 1019, 140 U.S.P.Q. 665, 668 (CCPA 1964)". [M.P.E.P §2107.01]

The specification does indeed provide utilities for the rAAV vectors of the present invention other than gene therapy protocols. For example, the specification describes the transfer of genes to mammalian cells via the viral vectors of the present invention for the purpose of evaluating transduction and gene expression (see the instant specification at e.g., page 27, lines 15 to 23; page 32, lines 11 to 31; and page 35, lines 11 to 13). The specification clearly points to the advantages of using rAAV vectors expressing the FACC gene, a therapeutic gene, the expression of which confers a phenotype which serves as a biological marker to detect gene transfer both in vitro and in vivo. (see the instant specification, page 43, lines 18 to 24). The specification further points to the use of rAAV vectors expressing the FACC gene to study in vitro gene complementation and functional correction of the FA defect, and the working examples demonstrate the successful application of the recombinant AAV vectors of the present invention to achieve this goal (see, the instant specification at page 39, line 18 to 31).

Further, as supported by the data presented in the instant specification and the enclosed Samulski Declaration, the recombinant AAV vectors of the present invention are clearly capable of transducing cells in vivo to achieve detectable levels of expression of whatever reporter or therapeutic gene product is incorporated into the recombinant viral vector. Thus, there is no reason to believe that the

specification does not support and enable the entire scope of the claimed recombinant viral vectors, including the use of the vectors in vivo and in vitro for purposes other than gene therapy.

Thus, contrary to the Examiner's contention, the specification clearly describes and enables utilities other than gene therapy for the recombinant viral vectors of the present invention. Therefore, the Examiner is wrong to examine the claims as if they were limited to a gene therapy utility requiring alleviation of disease symptoms. When examined in connection with their proper scope, i.e., gene transfer to mammalian cells in vivo and in vitro, it is clear that the claims are enabled. The data presented in the specification demonstrate the successful use of the recombinant adeno-associated viral vectors claimed for gene transfer and expression in vivo in mammals.

Applicants assert that when the evidence of record is analyzed in connection with the proper construction of the claims, the only conclusion that can be reached is that the claimed compositions are enabled within the meaning of Section 112. The instant specification is fully enabled for the pending claims. For all the aforementioned reasons, Applicant respectfully submits that the §112, first paragraph, enablement rejections be withdrawn.

CONCLUSION

Entry of the foregoing remarks into the file of the above-identified application is respectfully requested. Applicants believe that the invention defined by the claims

meets all the requirements for patentability. Withdrawal of all rejections and reconsideration of the amended claims so requested. An early allowance is earnestly sought.

Respectfully submitted,

Date August 13, 1998

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosure

Nicholas C. Kluge
Reg. No. 39,201